Endogenous pain modulation profiles among individuals with chronic pain

Relation to opioid use

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Abstract: It is generally assumed that individuals exhibiting high pain inhibition also tend to exhibit low pain facilitation, but little research has examined this association in individuals with pain. The aims of this cross-sectional study were 1) to examine the association between measures of conditioned pain modulation (CPM) and temporal summation (TS) in individuals with chronic pain and 2) to examine whether this association was moderated by demographic (age, sex), psychological (depression, catastrophizing), or medication-related (opioid use) variables. individuals (n = 190) with back or neck pain completed questionnaires and underwent a series of quantitative sensory testing (QST) procedures assessing CPM and TS. Results indicated that individuals with higher levels of CPM showed lower levels of TS, $r = -.20$, $p < .01$. Analyses, however, revealed that the magnitude of this association was substantially weaker among opioid users ($r = -.08$, ns) than non-users ($r = -.34$, $p < .01$). None of the demographic or psychological variables included in our study influenced the association between CPM and TS. The magnitude of CPM was lower for opioid users than non-users, suggesting that opioid use might dampen the functioning of endogenous pain-inhibitory systems, and might contribute to a discordance between measures of pain inhibition and pain facilitation.

Endogenous pain modulation profiles among individuals with chronic pain: Relation to opioid use

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Abstract

It is generally assumed that individuals exhibiting high pain inhibition also tend to exhibit low pain facilitation, but little research has examined this association in individuals with pain. The aims of this cross-sectional study were 1) to examine the association between measures of conditioned pain modulation (CPM) and temporal summation (TS) in individuals with chronic pain and 2) to examine whether this association was moderated by demographic (age, sex), psychological (depression, catastrophizing), or medication-related (opioid use) variables. individuals (n = 190) with back or neck pain completed questionnaires and underwent a series of quantitative sensory testing (QST) procedures assessing CPM and TS. Results indicated that individuals with higher levels of CPM showed lower levels of TS, r = -.20, $p < .01$. Analyses, however, revealed that the magnitude of this association was substantially weaker among opioid users (r = -.08, ns) than non-users (r = -.34, $p < .01$). None of the demographic or psychological variables included in our study influenced the association between CPM and TS. The magnitude of CPM was lower for opioid users than non-users, suggesting that opioid use might dampen the functioning of endogenous pain-inhibitory systems, and might contribute to a discordance between measures of pain inhibition and pain facilitation.

Perspective

Results of the present study indicated that greater endogenous pain-inhibitory capacity is associated with lower levels of pain facilitation. This association, however, was not significant among opioid users, suggesting that opioids might compromise the functioning and interrelationship between endogenous pain modulatory systems.

Keywords

Endogenous pain inhibition; pain facilitation; opioids; chronic pain

1.0. Introduction

It is well known that nociceptive signals can be modulated by central pain inhibitory and facilitatory processes [1, 8, 82]. These pain-modulatory processes operate at various levels of the central nervous system and are assumed to play a determining role in the manifestations of chronic pain and in shaping inter-individual variability in the trajectory of many persistent pain conditions [6, 25, 51, 83]. Considerable studies have been conducted using quantitative sensory testing (QST) to assess pain inhibition and pain facilitation [9, 19, 71]. For instance, conditioned pain modulation (CPM) and temporal summation (TS) paradigms have been used as indices of pain-inhibitory and pain-summation processes[1, 4, 8]. Evidence of impaired CPM and/or facilitated TS has been observed among individuals with a variety of chronic musculoskeletal, visceral, and neuropathic pain conditions (for reviews, see [6, 48, 71, 76]).

There has been growing interest in characterizing individuals with chronic pain based on their pain modulation profiles (PMPs) [4, 8, 56, 84, 86], as inter-individual variability in pain modulation has been shown to predict clinical outcomes such as development or worsening of pain after surgery [45, 55, 56]. Studies also found that TS is a predictor of responses to cyclooxygenase-2 (COX-2) inhibitors [3] and that CPM is a predictor of responses to topical nonsteroidal anti-inflammatory drugs (NSAID) [27] as well as pregabalin treatment [13, 87]. It has been argued that characterizing individuals with chronic pain based on their pain modulation profiles might provide valuable “mechanistic” information to clinicians in the context of pain assessment and individualized treatment selection [25, 56, 75, 84, 86].

One outstanding question in the literature on endogenous pain modulation is the manner in which pain-inhibitory processes (e.g., CPM) and pain-facilitatory processes (e.g., TS) inter-relate. For instance, some have hypothesized a concordance between these measures[84, 86], as individuals with low CPM would be expected to exhibit high TS, and vice versa. Psychophysical studies suggest that descending pain-inhibitory systems can modulate pain-facilitatory processes such as temporal summation [33, 64, 67]. To date, however, it remains unclear whether individual differences in CPM and TS are associated, and very little research has been conducted on the nature of the association between these measures of pain modulation among individuals with chronic pain.

One of the few studies that has grouped together clusters of individuals with pain on the basis of both pain inhibition and pain facilitation reported an interactive effect of these measures, with those who had a combination of poor CPM and elevated TS showing the worst pain after joint replacement surgery [56]. However, that study was not designed to evaluate the basal inter-correlation between CPM and TS, and it is unknown to what extent these factors tend to cluster within individual patients. Moreover, previous studies have shown that endogenous pain inhibition and pain summation may be influenced by a number of demographic variables, such as age and sex [37, 48, 76], and by psychological variables such as catastrophizing [34, 38, 57, 80] and negative affect [21, 39, 61], which suggests that any CPM-TS relationships could be influenced by such variables. Furthermore, a number of studies have also shown that medications, such as opioids, may also affect endogenous pain-modulatory processes [2, 60, 73]. Thus, there is reason to believe that some of these factors could contribute to

enhancing or decreasing the strength of the association between measures of pain inhibition and pain summation among individuals with pain.

The aims of this study were 1) to examine the association between measures of CPM and TS in a large cohort of individuals with chronic pain, 2) to examine the potential moderating role of demographic and psychological factors in the association between CPM and TS, and 3) to investigate the role of opioid use in the association between CPM and TS.

2.0. Methods

2.1. Participants

A sample of 190 individuals with chronic back or neck pain was included in this cross-sectional study. Participants were part of broader study project examining the psychophysical correlates of long-term opioid use. Although some data from the broader parent study were previously published [35], this is our first report specifically examining the association between measures of CPM and TS. Participants in the parent study were recruited via treating physicians at Brigham and Women's Hospital (BWH) and local posting of print advertisements around the BWH Pain Management Center. Participants met the following inclusion criteria: (1) chronic back or neck pain, (2) had been experiencing pain for at least 6 months (3) able to speak, read, and write in English. They were excluded if (4) they had cancer, bone disease, heart disease, or a neurological disease, or (5) cognitive limitations that precluded providing self-report data. Individuals with (6) any active addiction problem (i.e., substance use disorder) were not included in the present study given the current clinical practice guidelines and principles at the BWH Pain Center regarding the management of patients with

substance use disorder (SUD). Patients with active SUD are generally referred to a local addiction treatment facility before undergoing pain treatment at the Pain Center and before being eligible for study participation. For the purposes of the present report, (7) individuals taking non-opioid adjuvant medications in addition to prescription opioids, such as antidepressants, anticonvulsants or sedatives were excluded from the study sample given the potential influence of these medications on endogenous pain modulatory systems [5, 7, 36, 79, 89].

2.2. Procedure & measures

The Human Subjects Committee of BWH approved all study procedures. Interested participants underwent a telephone-based screening before coming in for the study visit. Upon arrival at the laboratory, participants underwent the process of providing informed consent, signed a consent form, and were asked to complete a demographic questionnaire, which included information about age, gender, and ethnicity. Participants also provided information on pain diagnosis and pain duration. They were then asked to report all the medications they were currently taking. Reports of medication were verified by a research assistant after the study session using the electronic medical record system, and published tables [24] were used to convert opioid doses into morphine equivalent daily doses (MEDD). In addition to providing this information, participants were asked to complete self-report questionnaires assessing pain and psychological variables, and then underwent a series of standardized quantitative sensory testing procedures (see below).

2.2.1. Clinical pain severity

The Brief Pain Inventory (BPI [74]) was used as a measure of chronic pain severity. On the BPI, participants were asked to rate their average level of pain intensity (i.e., over the past 24 hours) on a numeric rating scale (NRS) that ranged from 0 (no pain) to 10 (extreme pain). Participants were also asked to rate the degree to which pain interferes with various domains of functioning on a NRS that ranged from 0 (does not interfere) to 10 (completely interferes). The BPI has been shown to be a reliable and valid measure of pain severity and pain interference among individuals with chronic pain [46, 47, 74].

2.2.2. Pain catastrophizing

The Pain Catastrophizing Scale (PCS [68]) was used as a measure of catastrophic thinking about pain. The PCS contains 13 items describing different thoughts and feelings that individuals may experience when they are in pain. Participants were asked to reflect on past painful experiences and to indicate the degree to which they experienced each of 13 thoughts or feelings when experiencing pain, on a 5-point scale ranging from 0 (not at all) to 4 (all the time). Numerous studies have supported the reliability and the validity of the PCS as a measure of pain-related catastrophic thinking among individuals with chronic pain [26, 54, 70].

2.2.3. Depressive symptoms

The Beck Depression Inventory (BDI-II [10]) was used as a measure of depressive symptomatology. The BDI-II consists of 21 items describing various symptoms of depression, and participants choose statements that describe how they have been feeling over the past two weeks. Responses are summed to yield an overall index of

depressive symptoms. The BDI has been shown to be a reliable and valid index of depressive symptoms among individuals with chronic pain [58, 69,78].

2.2.4. Quantitative sensory testing (QST)

During the QST session, participants were seated comfortably in a reclining chair while they underwent a standardized battery of psychophysical pain testing procedures. A trained research assistant sat with participants throughout the QST session. The QST session involved assessment of warmth and cool thresholds, heat pain thresholds (HPTh), cold pain thresholds (CPTh), and heat pain tolerance (HPTo), all tested on the ventral forearm. Pressure pain thresholds (PPT) at the joint of the thumb were also assessed. For purposes of the present study, only the mechanical temporal summation of pain (TS) and conditioned pain modulation (CPM) procedures are described below.

2.2.4.1. Temporal summation

Participants underwent an assessment of mechanical temporal summation using a set of 7 custom-made weighted pinprick stimulators developed by the German research Network on Neuropathic Pain [62, 63]. These punctuate mechanical probes have a flat contact area of .2 mm in diameter, and exert forces between 8 and 512 mN. Punctate stimuli were delivered to the skin on the dorsum of the middle finger of the right hand. Participants were first familiarized with the procedure by undergoing a practice trial (on the palm of their hand) during which we determined the lowest force stimulator that produced a painful sensation (128 or 256 mN for most participants). This force was then used to apply a train of 10 stimuli at the rate of 1 per second for the assessment of temporal summation. Participants rated the painfulness of the first, fifth, and tenth stimulus on a 0 to 100 verbal pain intensity scale. An index of temporal

summation was derived by subtracting participants' 1st pinprick pain rating from the last (10th) pinprick pain rating. Higher (positive) scores represented higher levels of temporal summation (i.e., pain facilitation) [32, 35].

2.2.4.2. Conditioned pain modulation

In order to assess CPM, baseline pressure pain thresholds (PPTs) were first assessed using a handheld digital pressure algometer (Somedic, Hörby, Sweden) on the right upper trapezius, approximately 2 cm from the acromioclavicular joint. Given that participants had previously been familiarized with pressure pain threshold (PPT) assessment (assessed at the thumb) earlier during the QST session, CPM testing did not involve any practice trial. During baseline assessment of PPT at the trapezius, mechanical force was applied using a 0.5-cm^2 probe covered with polypropylene pressure-transducing material. Pressure was increased at a steady rate of 30 kPa/s until the subject indicated that the pressure was "first perceived as painful." Immediately following the assessment of PPT, participants underwent a cold pressor test (CPT). During the CPT, participants immersed their contralateral (left) hand up to the wrist in a circulating cold water bath maintained at 4°C, a water temperature used as conditioning stimulus in many previous CPM studies [12, 38, 64]. Twenty seconds following hand immersion, PPT was reassessed on the right trapezius (i.e., the same site as baseline assessment). Participants were asked to remove their arm from the water 30 seconds after arm immersion. A second CPM trial was conducted two minutes after the end of the first CPM trial. The use of a 2-minute rest period between CPM trials is consistent with procedures that have been used in several previous CPM studies using the cold pressor test as the conditioning stimulus [30, 33, 38]. Assessing CPM twice is also

consistent with recommendations on CPM testing. [85] For each of the CPM trials, a CPM index was derived by calculating the percent ratio of PPT during CPT to PPT prior to CPT. Scores from these two CPM trials were averaged, and higher CPM scores represented greater pain-inhibitory capacity.[28, 31, 65, 85]

3.0. Data Reduction and Analysis

All data were analyzed using IBM-SPSS v.21 (Chicago, IL, USA). The alpha level for significance was set to $p < .05$ for all analyses, and p-values above .05 are labeled in the Results section as NS (non-significant). Descriptive data for continuous variables were presented as means and standard deviations, and data for categorical variables were presented as percentages. Data for one of the CPM trials were missing for 7% of participants (i.e., 13/190). For these participants, data from the first CPM trial were used for the computation of the final CPM index.

Prior to conducting the primary study analyses, the potential confounding influence of ethnicity, clinical pain intensity, pain interference, and pain duration on CPM and TS was examined. Variables associated either with CPM or TS were retained as covariates in subsequent analyses.

A Pearson correlation was first computed to examine the association between CPM and TS. Pearson correlations were then computed to examine the association between psychological factors (i.e., catastrophizing, depressive symptoms) and endogenous pain modulation measures (i.e., CPM, TS), and independent samples t-tests were used to examine whether CPM and TS scores varied as a function of participant sex (i.e., men/women) and opioid status (i.e., opioid users/non-users).

In order to examine the potential moderating role of age, sex, opioid status, and psychological factors in the association between CPM and TS, five distinct moderation analyses were conducted using the PROCESS macro developed by Hayes et al. [43] For each of these moderation analyses, the TS index was used as the dependent variable, and two-way interaction terms between the CPM index and potential moderators (i.e., age, sex, opioid status, catastrophizing, depressive symptoms) were specified after inclusion of appropriate main effects. Any significant two-way interaction effect would suggest that the association between CPM and TS is moderated by participant age, sex, opioid status, catastrophizing, or depressive symptoms. Bias-corrected 95% confidence intervals (CI) were generated based on 5,000 bootstrap resamples, and CIs were presented along with p-values to interpret the significance of interaction/moderation effects. As recommended, moderation effects were considered significant in the case zero was not included within the CIs. Bootstrapping has been widely recommended because it improves power, but it was estimated that our sample size would be sufficient in order to detect medium-to-large effects using bootstrapping with two independent variables (IVs), an alpha set to .05, and a power of .80.[43]

4.0. Results

4.1. Descriptive statistics

Descriptive statistics are presented in Table 1. In the present sample, 64 % (n = 122) of participants were taking opioids (average daily opioid dose = 101.0 morphine equivalents; SD = 114.8).

Prior to conducting primary analyses, the potential confounding influence of ethnicity, clinical pain intensity, pain interference, and pain duration on primary study

variables (i.e., CPM, TS) was examined. For opioid users, the influence of daily opioid dose on CPM and TS was also examined. None of these variables were significantly associated with either CPM or TS (see Table 2). Opioid users and non-users differed significantly on measures of clinical pain intensity ($t(176) = -7.3$, $p < .01$) and pain interference ($t(154) = -8.4$, $p < .01$), but not in pain duration.

4.2. Association between psychological factors and endogenous pain modulation

Table 2 also shows the correlations between psychological factors and endogenous pain modulation measures. Correlational analyses revealed a marginally significant negative association between catastrophizing and CPM ($r = -.14$, $p = .05$), indicating that higher levels of catastrophizing were associated with lower CPM. A significant positive correlation was found between catastrophizing and TS ($r = .15$, $p < .05$). Depressive symptoms were not significantly associated with either CPM or TS.

Independent samples t-tests were used to examine whether CPM and TS scores varied as a function of participant sex (i.e., men/women) and opioid status (i.e., opioid users/non-users). Results indicated that there were no significant sex differences either in CPM ($t(188) = 1.8$, NS) or TS ($t(188) = -.62$, NS). Results of t-tests, however, indicated a marginally significant difference in CPM as a function of opioid status, with lower CPM scores for opioid users than non-users, $t(188) = 2.1$, $p < .05$. Opioid users and non-users did not differ significantly on the TS index, $t(188) = -0.10$, NS (see Figures 1 and 2).

4.3. Association between CPM and TS

A Pearson correlation was computed to examine the association between CPM and TS. Results revealed a significant negative correlation between CPM and TS

scores (r = -.20, p < .01), indicating that higher levels of CPM were associated with lower levels of temporal summation.

4.4. Moderators of the association between CPM and TS

As noted previously, five distinct bootstrapped moderation analyses were conducted to examine whether age, sex, opioid status, catastrophizing, or depressive symptoms moderated the association between CPM and TS. Results from these analyses indicated no significant 2-way interactions between CPM and participant age (B = .001, SE = .004, NS), sex (B = .053, SE = .099, NS), catastrophizing (B = -.006, SE = .004, NS), or depressive symptoms (B = -.001, SE = .006, NS). The two-way interaction effect between CPM and opioid status, however, was significant (B = .194, SE = .091, p < .05; LLCI = .014; ULCI = .375), indicating that the association between CPM and TS was moderated by participants' opioid status. Simple slope analyses were subsequently conducted in order to probe the interaction of CPM and opioid status on TS. As can be seen from Figure 3, the association between CPM and TS varied as a function of participants' opioid status (i.e., opioid users vs non-users). Results revealed a significant association between CPM and TS for non-users (r = -.34, p < .01), but not for opioid users (r = -.08, NS).

5.0. Discussion

Results of this study indicated that greater endogenous pain-inhibitory capacity is associated with lower levels of pain summation. Further, a moderation analysis revealed that the magnitude of this association differed significantly as a function of participants' opioid status, with opioid use appearing to reduce the magnitude of the inverse relationship between CPM and TS. None of the demographic or psychologic variables

included in the present study were found to moderate the association between CPM and TS.

The association that was found between CPM and TS is generally consistent with heuristic models of endogenous pain modulation that implicitly assume a certain degree of concordance between measures of pain inhibition and facilitation [4, 20, 27, 66, 84, 86]. For instance, individuals exhibiting either high pain inhibition (high CPM), low pain summation (low TS), or both, have been collectively described as having an "antinociceptive" pain modulation phenotype, as opposed to a pro-nociceptive phenotype characterized by high TS and low CPM [40, 86]. It is also noteworthy that individuals with chronic pain conditions characterized by "dysfunctional" pain modulation tend to show both decrements in CPM and elevations in TS relative to controls [1, 8, 22, 23, 66]. On the basis of this model, one would expect an inverse association between indices of endogenous pain inhibition and endogenous pain facilitation, which is what we observed in the present study. In addition, two recent studies found that roughly 30 % of individuals with "normal" or "higher-than-average" CPM levels were characterized by low levels of TS [56, 75], which is also consistent with our results.

Interestingly, the present study found an association between measures of CPM and TS selectively among individuals who are not using opioids. While a number of factors might account for the altered association between CPM and TS among opioid users, our data suggest that this might be due at least in part to the potentially disruptive effects of exogenous opioids on individuals' endogenous pain-inhibitory capacity. Consistent with previous work [29, 59], we found that the magnitude of CPM was lower for opioid users than non-users, suggesting that opioid use might dampen the functioning

of endogenous pain-inhibitory systems. Interestingly, several recent experimental studies have found that acute opioid administration may enhance endogenous pain inhibition [2, 53], and other reports of short-term administration have suggested minimal effects [73]. Collectively, these findings may suggest that the impact of opioid use on indices of pain inhibition shows a biphasic time course, with acute potentiation of CPM followed by long-term decrements of CPM. There is now compelling evidence both from preclinical [15, 50] and clinical [77, 88] studies that opioid use, over time, may progressively lead to enduring neuroplastic changes at various levels of the central nervous system (CNS), including within neural pathways known to be involved in endogenous pain inhibition. To the extent that endogenous pain-inhibitory systems exert a modulatory influence upon pain summation [6, 25, 41, 81], opioid-induced disruption of pain-inhibitory function might compromise the expected association between pain inhibition and pain facilitation, as observed among opioid users included in the present study. Although speculative, a disruption of pain-inhibitory function as a result of repeated opioid use might contribute to enhanced descending facilitatory activity and, in turn, to opioid-induced hyperalgesia (OIH), a phenomenon observed both experimentally and clinically [16, 17, 49, 72]. The observational nature of our study design prevents from concluding that opioid use caused hyperalgesic responses (i.e., opioid-induced hyperalgesia). However, the significantly lower pain-inhibitory (i.e., CPM) function and heightened clinical pain intensity levels observed among opioid users compared to non-users provide partial support for this notion. Previous studies among individuals with chronic pain have also observed disruptions in CPM [28, 60, 90] and heightened clinical pain intensity levels [17, 18] among long-term opioid users. However, given that these studies were also based on

observational study designs, research will be needed to determine whether a disruption of the association between pain-inhibitory and pain-facilitatory mechanisms may contribute to the development of opioid-induced hyperalgesia among individuals who initiate opioid therapy.

The findings of the present study have not only implications for conceptual models of endogenous pain modulation, but also for the assessment of pain-modulatory profiles in treatment settings. For instance, the modest overlap (i.e., concordance) between measures CPM and TS suggests considerable inter-individual heterogeneity within each of the pain modulation profiles. Consequently, in clinic settings, these two measures should not be used interchangeably to derive inferences about individuals' pain modulation. The predictive consideration of both CPM and TS paradigms is likely to yield a more reliable and comprehensive assessment of pain modulation profiles [55]. Our findings also suggest that a certain "discordance" between measures of endogenous pain inhibition (i.e., CPM) and pain facilitation (i.e., TS) might be more particularly pronounced among specific subgroups of individuals with chronic pain, such as those using opioid medication. Given that the coupling of high pain inhibition and low pain facilitation is viewed as an optimal pain modulation profile (i.e., an "antinociceptive" PMP) with the potential for buffering against negative pain-related outcomes [25, 84, 86], the putative deleterious impact of opioids on individuals' pain modulation profiles should be considered over the course of treatment selection, either in the context of perioperative or chronic pain management. Future research should also examine whether the association between pain inhibition and pain facilitation is enhanced when individuals

are discontinuing or tapering off opioid medication, as well as the time course of these putative shifts in pain modulation produced by changes in opioid treatments.

A number of limitations must be considered when interpreting the present findings. First, this study report is based on a convenience sample, which limited our explanatory reach in accounting for some of the findings that were reported. Second, due to the cross-sectional nature of the study design, individuals' levels of CPM and TS were assessed only at a single point in time. While these two measures have been found to be relatively stable over time [11, 14, 42, 44, 52], future studies involving repeated assessment of CPM and TS would allow one to derive more reliable inferences about the magnitude of the association between these two forms of endogenous pain modulation. Third, participants in the present study were taking relatively high doses of opioids considering recent changes in opioid prescribing guidelines [24]. Daily opioid doses were neither associated with CPM nor TS, but further studies will need to determine whether our findings can be generalized to patients taking lower opioid doses. It will also be important to further evaluate the influence of opioid dose and opioid use duration to the functioning of endogenous pain modulation systems. Fourth, individuals taking non-opioid analgesic medications were not included in the analyses. While this may be seen as a methodological strength, as it permitted us to rule out the influence of non-opioid medication on endogenous pain modulation, this places limits on the generalizability of our findings. Fifth, we did not measure potentially important variables, such as the duration of opioid therapy or the recency of opioid use in relation to QST. Future studies should control for inter-individual differences in these variables as they might influence measures of pain modulation. Finally, CPM was derived only on

the basis of the cold pressor test and pressure pain stimuli. Replication of our findings using other methods or CPM paradigms (i.e., using other conditioning and/or test stimuli) [44] is warranted before drawing more firm conclusions regarding the association between CPM and TS.

Conclusion

Findings from the present study provide new insights into the association between endogenous pain-inhibitory and pain summation systems, showing an inverse relationship between CPM and TS among individuals with chronic pain. That is, those exhibiting higher levels of CPM showed lower levels of TS. While the coupling of high pain inhibition and low pain facilitation is viewed as an optimal endogenous pain modulation profile that may buffer against negative pain-related outcomes [25, 84], the present findings suggest that opioid use might disrupt endogenous pain-inhibitory function and, in turn, the association between endogenous pain-inhibitory (i.e., CPM) and pain-facilitatory (TS) systems. Given that an impaired association between pain-inhibitory and pain-facilitatory systems is expected to increase individuals' vulnerability to poor pain-related outcomes [25, 56, 84], further research will be needed to identify the factors that may impair the interrelationship between these endogenous pain modulatory systems. Research will also be needed to determine whether a disruption of the association between pain-inhibitory and pain-facilitatory mechanisms may contribute to long-term sensitization and hyperalgesic responses (i.e., opioid-induced hyperalgesia) among opioid users. Research in this area would provide additional insights into the potentially deleterious impact of opioids on endogenous pain

modulation systems, and would have implications for the management of individuals with pain conditions.

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Figure Legends

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Sample characteristics and descriptive data for main study variables

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Conditioned pain modulation scores for opioid users and non-users

Figure 2
Temporal summation of pain scores for opioid users and non-users

Figure 3
Association between conditioned pain modulation and temporal summation as a function of individuals' opioid status

Figure 1
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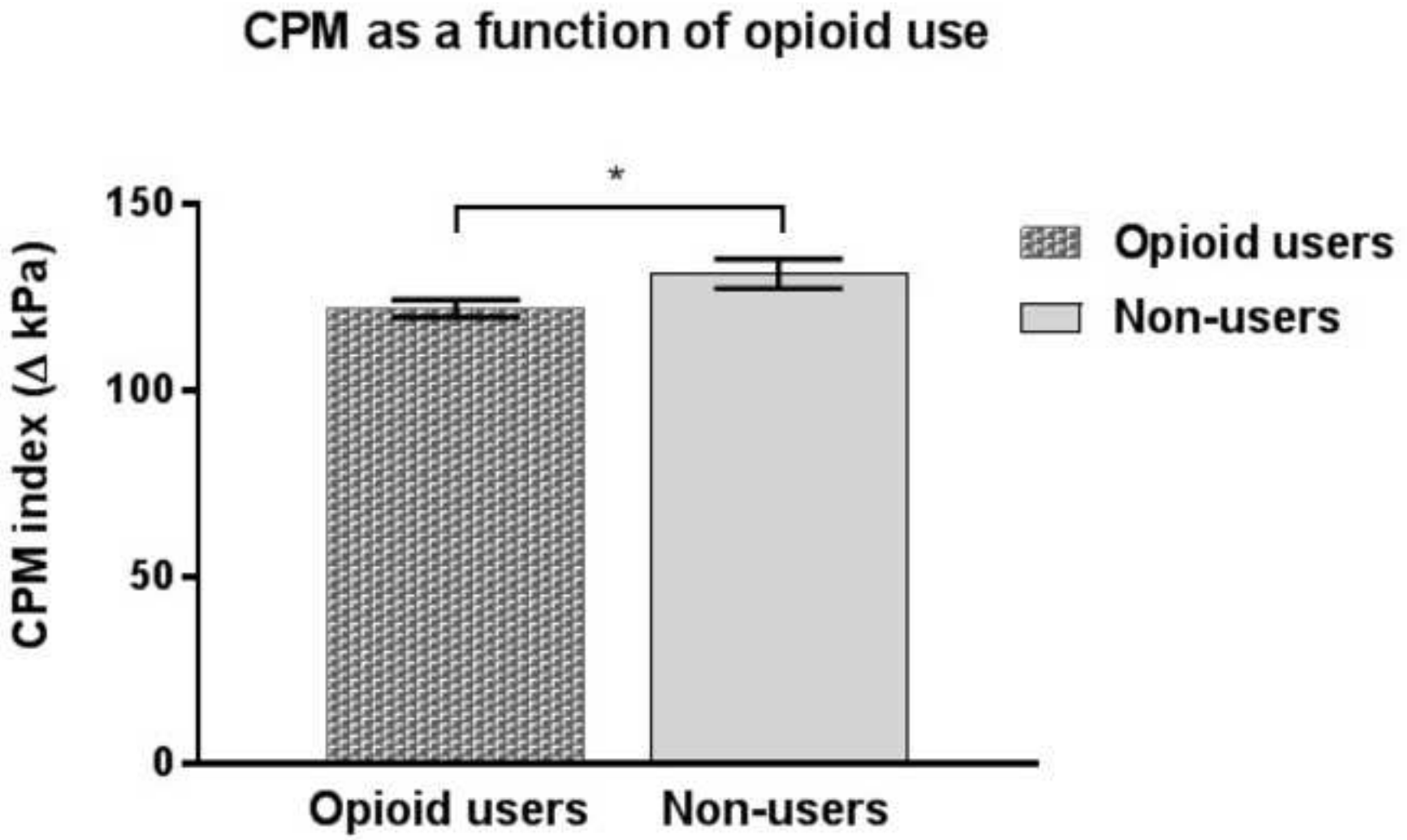

Fig. 1. Conditioned pain modulation (CPM) scores for opioid users and non-users (mean ± SEM). The CPM index represents the average of CPM trials; * $p < .05$

Figure 2
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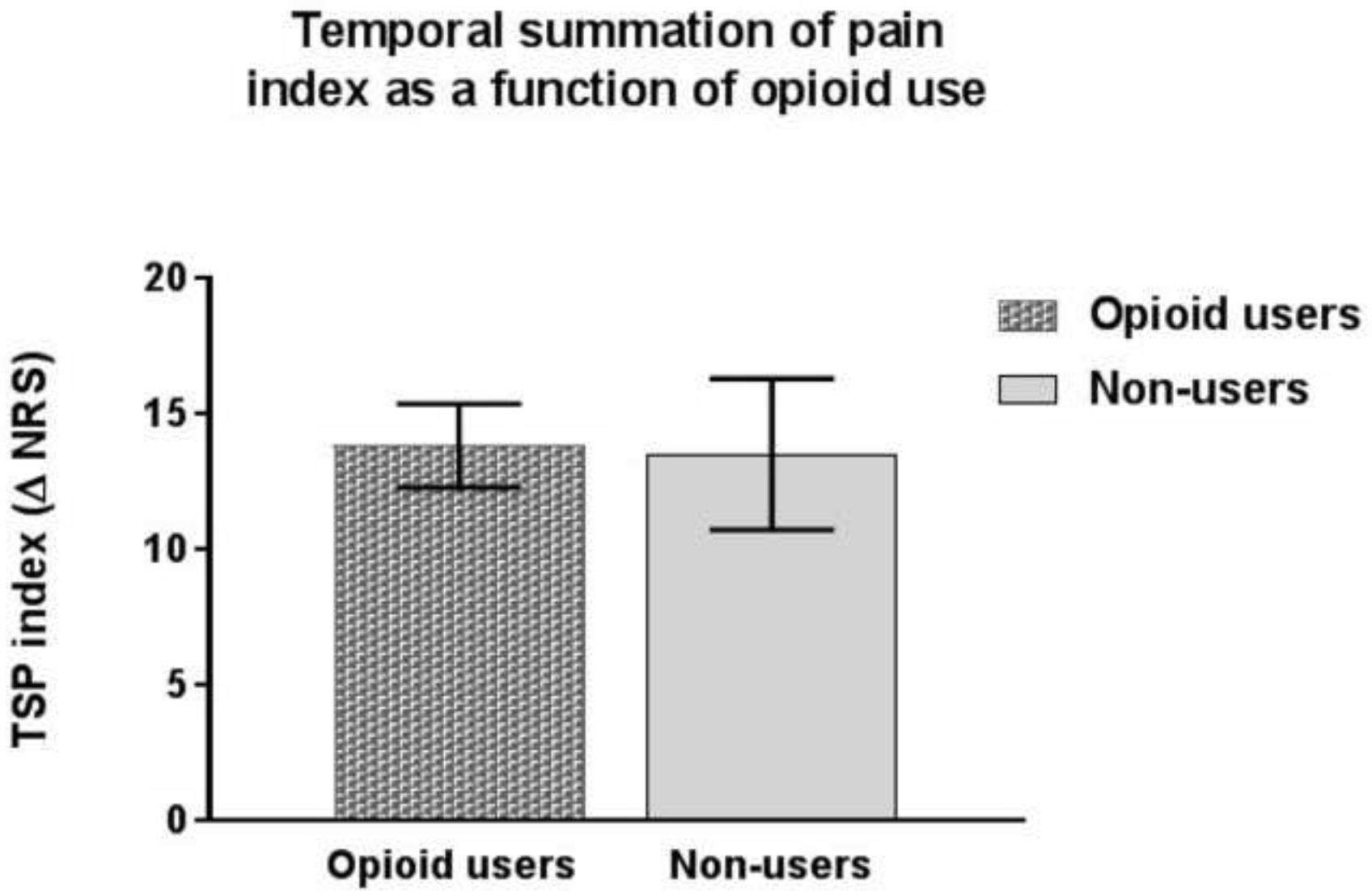

Fig. 2. Temporal summation of pain (TSP) scores for opioid users and non-users (mean ± SEM).

Figure 3
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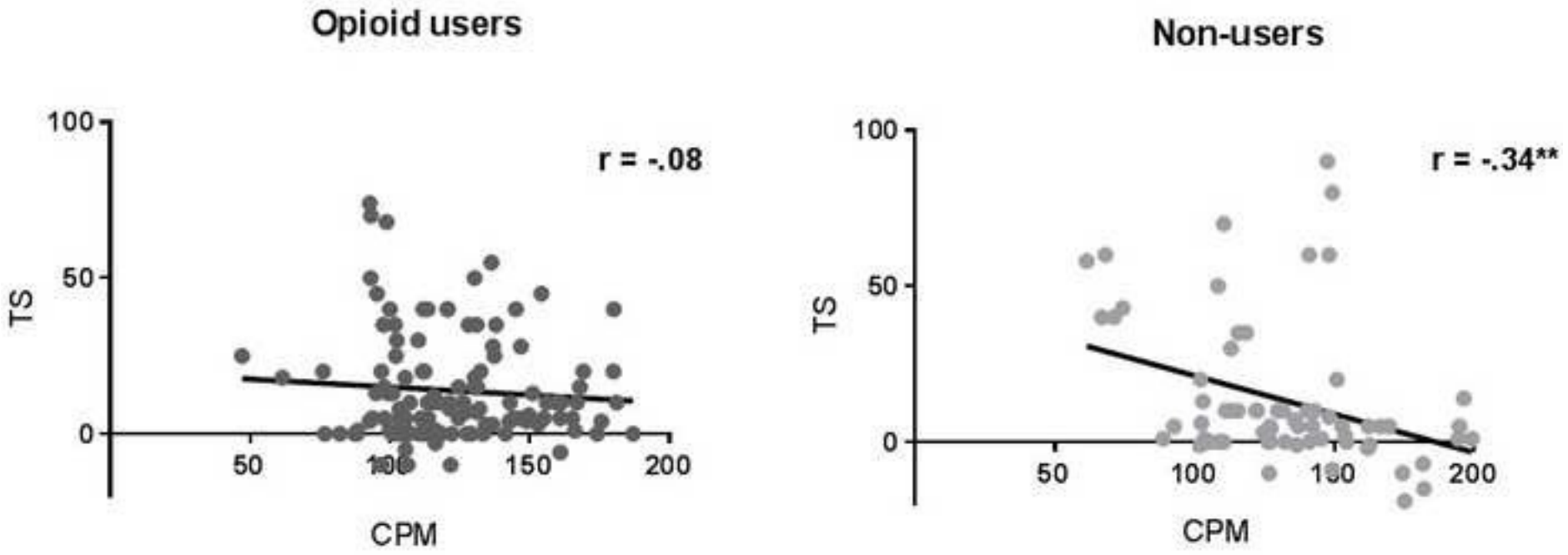

Fig. 3. Association between conditioned pain modulation (CPM) and temporal summation (TSP) as a function of patient opioid status. ** $p < .01$

Table 1

Table 1
Sample characteristics and descriptive data for main study variables

Variables	
Age	49.5 ± 10.9
Sex (% women)	43 %
Ethnicity (% white)	65 %
Pain duration (years)	10.8 ± 8.6
Pain location	
Back or neck pain	100 %
Radiating pain; lower	32 %
Radiating pain; upper	47 %
Pain intensity (BPI)	5.0 ± 2.4
Pain interference (BPI)	4.3 ± 2.9
Catastrophizing (PCS)	20.0 ± 12.1
Depressive symptoms (BDI)	11.6 ± 8.3

Note. ± represents standard deviations; BPI: Brief Pain Inventory; PCS: Pain Catastrophizing Scale; BDI: Beck Depression Inventory; Lower refers to legs and feet. Upper refers to shoulders and arms

Table 2

Table 2
Correlations among study measures

	1	2	3	4	5	6	7	8	9
1. Age	-	-.06	.11	-.37**	-.27**	-.31**	-.18**	.13	.02
2. Opioid dose†		-	-.12	.08	-.05	-.10	-.24	.03	-.13
3. Pain duration			-	.29*	.19	.18	.13	-.24	.18
4. Pain intensity (BPI)				-	.71**	.51**	.32**	-.10	.07
5. Pain interference (BPI)					-	.46**	.39**	-.04	.00
6. Catastrophizing (PCS)						-	.41**	-.14	.15*
7. Depressive symptoms (BDI)							-	.01	.00
8. Conditioned pain modulation								-	-.20**
9. Temporal summation									-

** Correlation is significant at the .01 level. * Correlation is significant at the .05 level. † Only among opioid users; BPI: Brief Pain Inventory; PCS: Pain Catastrophizing Scale; BDI: Beck Depression Inventory

Table 3

Table 3
Pressure pain thresholds and cold water pain during the conditioned pain modulation (CPM) test

	Opioid users	Non-users	*p*
CPM: Trial 1			
PPTh-Pre	373.5 (195.9)	326.1 (120.2)	< .05
Cold water pain	52.2 (24.9)	64.35 (26.5)	ns
PPTh-Post	448.3 (234.9)	422.8 (160.5)	ns
CPM: Trial 2			
PPTh-Pre	449.7 (223.1)	331.9 (120.9)	< .05
Cold water pain	58.2 (26.3)	68.7 (25.1)	ns
PPTh-Post	517.3 (260.7)	388.1 (137.9)	< .05

Note: PPTh-Pre: pressure pain thresholds before the water bath; Cold water pain: pain ratings during the water bath; PPTh-Pre: Pressure pain thresholds 20 seconds after cold pain (i.e., water bath) onset; Numbers in parentheses are standard deviations.

Table 4
Pinprick pain ratings during the temporal summation of pain (TSP) test

	Opioid users	Non-users	*p*
TSP			
1st stimulus	13.3 (14.3)	16.3 (16.8)	ns
10th stimulus	27.2 (23.9)	29.8 (29.4)	ns

Note: 1st stimulus refers to the pain rating (0-100) provided immediately after the first stimulus; 10th stimulus: Refers to the pain rating (0-100) provided immediately after the tenth stimulus.

Endogenous pain modulation profiles among individuals with chronic pain: Relation to opioid use

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Abstract

It is generally assumed that individuals exhibiting high pain inhibition also tend to exhibit low pain facilitation, but little research has examined this association in individuals with pain. The aims of this cross-sectional study were 1) to examine the association between measures of conditioned pain modulation (CPM) and temporal summation (TS) in individuals with chronic pain and 2) to examine whether this association was moderated by demographic (age, sex), psychological (depression, catastrophizing), or medication-related (opioid use) variables. individuals (n = 190) with back or neck pain completed questionnaires and underwent a series of quantitative sensory testing (QST) procedures assessing CPM and TS. Results indicated that individuals with higher levels of CPM showed lower levels of TS, r = -.20, $p < .01$. Analyses, however, revealed that the magnitude of this association was substantially weaker among opioid users (r = -.08, ns) than non-users (r = -.34, $p < .01$). None of the demographic or psychological variables included in our study influenced the association between CPM and TS. The magnitude of CPM was lower for opioid users than non-users, suggesting that opioid use might dampen the functioning of endogenous pain-inhibitory systems, and might contribute to a discordance between measures of pain inhibition and pain facilitation.

Perspective

Results of the present study indicated that greater endogenous pain-inhibitory capacity is associated with lower levels of pain facilitation. This association, however, was not significant among opioid users, suggesting that opioids might compromise the functioning and interrelationship between endogenous pain modulatory systems.

Keywords

Endogenous pain inhibition; pain facilitation; opioids; chronic pain

1.0. Introduction

It is well known that nociceptive signals can be modulated by central pain inhibitory and facilitatory processes [1, 8, 82]. These pain-modulatory processes operate at various levels of the central nervous system and are assumed to play a determining role in the manifestations of chronic pain and in shaping inter-individual variability in the trajectory of many persistent pain conditions [6, 25, 51, 83]. Considerable studies have been conducted using quantitative sensory testing (QST) to assess pain inhibition and pain facilitation [9, 19, 71]. For instance, conditioned pain modulation (CPM) and temporal summation (TS) paradigms have been used as indices of pain-inhibitory and pain-summation processes[1, 4, 8]. Evidence of impaired CPM and/or facilitated TS has been observed among individuals with a variety of chronic musculoskeletal, visceral, and neuropathic pain conditions (for reviews, see [6, 48, 71, 76]).

There has been growing interest in characterizing individuals with chronic pain based on their pain modulation profiles (PMPs) [4, 8, 56, 84, 86], as inter-individual variability in pain modulation has been shown to predict clinical outcomes such as development or worsening of pain after surgery [45, 55, 56]. Studies also found that TS is a predictor of responses to cyclooxygenase-2 (COX-2) inhibitors [3] and that CPM is a predictor of responses to topical nonsteroidal anti-inflammatory drugs (NSAID) [27] as well as pregabalin treatment [13, 87]. It has been argued that characterizing individuals with chronic pain based on their pain modulation profiles might provide valuable “mechanistic” information to clinicians in the context of pain assessment and individualized treatment selection [25, 56, 75, 84, 86].

One outstanding question in the literature on endogenous pain modulation is the manner in which pain-inhibitory processes (e.g., CPM) and pain-facilitatory processes (e.g., TS) inter-relate. For instance, some have hypothesized a concordance between these measures[84, 86], as individuals with low CPM would be expected to exhibit high TS, and vice versa. Psychophysical studies suggest that descending pain-inhibitory systems can modulate pain-facilitatory processes such as temporal summation [33, 64, 67]. To date, however, it remains unclear whether individual differences in CPM and TS are associated, and very little research has been conducted on the nature of the association between these measures of pain modulation among individuals with chronic pain.

One of the few studies that has grouped together clusters of individuals with pain on the basis of both pain inhibition and pain facilitation reported an interactive effect of these measures, with those who had a combination of poor CPM and elevated TS showing the worst pain after joint replacement surgery [56]. However, that study was not designed to evaluate the basal inter-correlation between CPM and TS, and it is unknown to what extent these factors tend to cluster within individual patients. Moreover, previous studies have shown that endogenous pain inhibition and pain summation may be influenced by a number of demographic variables, such as age and sex [37, 48, 76], and by psychological variables such as catastrophizing [34, 38, 57, 80] and negative affect [21, 39, 61], which suggests that any CPM-TS relationships could be influenced by such variables. Furthermore, a number of studies have also shown that medications, such as opioids, may also affect endogenous pain-modulatory processes [2, 60, 73]. Thus, there is reason to believe that some of these factors could contribute to

enhancing or decreasing the strength of the association between measures of pain inhibition and pain summation among individuals with pain.

The aims of this study were 1) to examine the association between measures of CPM and TS in a large cohort of individuals with chronic pain, 2) to examine the potential moderating role of demographic and psychological factors in the association between CPM and TS, and 3) to investigate the role of opioid use in the association between CPM and TS.

2.0. Methods

2.1. Participants

A sample of 190 individuals with chronic back or neck pain was included in this cross-sectional study. Participants were part of broader study project examining the psychophysical correlates of long-term opioid use. Although some data from the broader parent study were previously published [35], this is our first report specifically examining the association between measures of CPM and TS. Participants in the parent study were recruited via treating physicians at Brigham and Women's Hospital (BWH) and local posting of print advertisements around the BWH Pain Management Center. Participants met the following inclusion criteria: (1) chronic back or neck pain, (2) had been experiencing pain for at least 6 months (3) able to speak, read, and write in English. They were excluded if (4) they had cancer, bone disease, heart disease, or a neurological disease, or (5) cognitive limitations that precluded providing self-report data. Individuals with (6) any active addiction problem (i.e., substance use disorder) were not included in the present study given the current clinical practice guidelines and principles at the BWH Pain Center regarding the management of patients with

substance use disorder (SUD). Patients with active SUD are generally referred to a local addiction treatment facility before undergoing pain treatment at the Pain Center and before being eligible for study participation. For the purposes of the present report, (7) individuals taking non-opioid adjuvant medications in addition to prescription opioids, such as antidepressants, anticonvulsants or sedatives were excluded from the study sample given the potential influence of these medications on endogenous pain modulatory systems [5, 7, 36, 79, 89].

2.2. Procedure & measures

The Human Subjects Committee of BWH approved all study procedures. Interested participants underwent a telephone-based screening before coming in for the study visit. Upon arrival at the laboratory, participants underwent the process of providing informed consent, signed a consent form, and were asked to complete a demographic questionnaire, which included information about age, gender, and ethnicity. Participants also provided information on pain diagnosis and pain duration. They were then asked to report all the medications they were currently taking. Reports of medication were verified by a research assistant after the study session using the electronic medical record system, and published tables [24] were used to convert opioid doses into morphine equivalent daily doses (MEDD). In addition to providing this information, participants were asked to complete self-report questionnaires assessing pain and psychological variables, and then underwent a series of standardized quantitative sensory testing procedures (see below).

2.2.1. Clinical pain severity

The Brief Pain Inventory (BPI [74]) was used as a measure of chronic pain severity. On the BPI, participants were asked to rate their average level of pain intensity (i.e., over the past 24 hours) on a numeric rating scale (NRS) that ranged from 0 (no pain) to 10 (extreme pain). Participants were also asked to rate the degree to which pain interferes with various domains of functioning on a NRS that ranged from 0 (does not interfere) to 10 (completely interferes). The BPI has been shown to be a reliable and valid measure of pain severity and pain interference among individuals with chronic pain [46, 47, 74].

2.2.2. Pain catastrophizing

The Pain Catastrophizing Scale (PCS [68]) was used as a measure of catastrophic thinking about pain. The PCS contains 13 items describing different thoughts and feelings that individuals may experience when they are in pain. Participants were asked to reflect on past painful experiences and to indicate the degree to which they experienced each of 13 thoughts or feelings when experiencing pain, on a 5-point scale ranging from 0 (not at all) to 4 (all the time). Numerous studies have supported the reliability and the validity of the PCS as a measure of pain-related catastrophic thinking among individuals with chronic pain [26, 54, 70].

2.2.3. Depressive symptoms

The Beck Depression Inventory (BDI-II [10]) was used as a measure of depressive symptomatology. The BDI-II consists of 21 items describing various symptoms of depression, and participants choose statements that describe how they have been feeling over the past two weeks. Responses are summed to yield an overall index of

depressive symptoms. The BDI has been shown to be a reliable and valid index of depressive symptoms among individuals with chronic pain [58, 69, 78].

2.2.4. Quantitative sensory testing (QST)

During the QST session, participants were seated comfortably in a reclining chair while they underwent a standardized battery of psychophysical pain testing procedures. A trained research assistant sat with participants throughout the QST session. The QST session involved assessment of warmth and cool thresholds, heat pain thresholds (HPTh), cold pain thresholds (CPTh), and heat pain tolerance (HPTo), all tested on the ventral forearm. Pressure pain thresholds (PPT) at the joint of the thumb were also assessed. For purposes of the present study, only the mechanical temporal summation of pain (TS) and conditioned pain modulation (CPM) procedures are described below.

2.2.4.1. Temporal summation

Participants underwent an assessment of mechanical temporal summation using a set of 7 custom-made weighted pinprick stimulators developed by the German research Network on Neuropathic Pain [62, 63]. These punctuate mechanical probes have a flat contact area of .2 mm in diameter, and exert forces between 8 and 512 mN. Punctate stimuli were delivered to the skin on the dorsum of the middle finger of the right hand. Participants were first familiarized with the procedure by undergoing a practice trial (on the palm of their hand) during which we determined the lowest force stimulator that produced a painful sensation (128 or 256 mN for most participants). This force was then used to apply a train of 10 stimuli at the rate of 1 per second for the assessment of temporal summation. Participants rated the painfulness of the first, fifth, and tenth stimulus on a 0 to 100 verbal pain intensity scale. An index of temporal

summation was derived by subtracting participants' 1st pinprick pain rating from the last (10th) pinprick pain rating. Higher (positive) scores represented higher levels of temporal summation (i.e., pain facilitation) [32, 35].

2.2.4.2. Conditioned pain modulation

In order to assess CPM, baseline pressure pain thresholds (PPTs) were first assessed using a handheld digital pressure algometer (Somedic, Hörby, Sweden) on the right upper trapezius, approximately 2 cm from the acromioclavicular joint. Given that participants had previously been familiarized with pressure pain threshold (PPT) assessment (assessed at the thumb) earlier during the QST session, CPM testing did not involve any practice trial. During baseline assessment of PPT at the trapezius, mechanical force was applied using a 0.5-cm^2 probe covered with polypropylene pressure-transducing material. Pressure was increased at a steady rate of 30 kPa/s until the subject indicated that the pressure was "first perceived as painful." Immediately following the assessment of PPT, participants underwent a cold pressor test (CPT). During the CPT, participants immersed their contralateral (left) hand up to the wrist in a circulating cold water bath maintained at 4°C, a water temperature used as conditioning stimulus in many previous CPM studies [12, 38, 64]. Twenty seconds following hand immersion, PPT was reassessed on the right trapezius (i.e., the same site as baseline assessment). Participants were asked to remove their arm from the water 30 seconds after arm immersion. A second CPM trial was conducted two minutes after the end of the first CPM trial. The use of a 2-minute rest period between CPM trials is consistent with procedures that have been used in several previous CPM studies using the cold pressor test as the conditioning stimulus [30, 33, 38]. Assessing CPM twice is also

consistent with recommendations on CPM testing. [85] For each of the CPM trials, a CPM index was derived by calculating the percent ratio of PPT during CPT to PPT prior to CPT. Scores from these two CPM trials were averaged, and higher CPM scores represented greater pain-inhibitory capacity.[28, 31, 65, 85]

3.0. Data Reduction and Analysis

All data were analyzed using IBM-SPSS v.21 (Chicago, IL, USA). The alpha level for significance was set to $p < .05$ for all analyses, and p-values above .05 are labeled in the Results section as NS (non-significant). Descriptive data for continuous variables were presented as means and standard deviations, and data for categorical variables were presented as percentages. Data for one of the CPM trials were missing for 7% of participants (i.e., 13/190). For these participants, data from the first CPM trial were used for the computation of the final CPM index.

Prior to conducting the primary study analyses, the potential confounding influence of ethnicity, clinical pain intensity, pain interference, and pain duration on CPM and TS was examined. Variables associated either with CPM or TS were retained as covariates in subsequent analyses.

A Pearson correlation was first computed to examine the association between CPM and TS. Pearson correlations were then computed to examine the association between psychological factors (i.e., catastrophizing, depressive symptoms) and endogenous pain modulation measures (i.e., CPM, TS), and independent samples t-tests were used to examine whether CPM and TS scores varied as a function of participant sex (i.e., men/women) and opioid status (i.e., opioid users/non-users).

In order to examine the potential moderating role of age, sex, opioid status, and psychological factors in the association between CPM and TS, five distinct moderation analyses were conducted using the PROCESS macro developed by Hayes et al. [43] For each of these moderation analyses, the TS index was used as the dependent variable, and two-way interaction terms between the CPM index and potential moderators (i.e., age, sex, opioid status, catastrophizing, depressive symptoms) were specified after inclusion of appropriate main effects. Any significant two-way interaction effect would suggest that the association between CPM and TS is moderated by participant age, sex, opioid status, catastrophizing, or depressive symptoms. Bias-corrected 95% confidence intervals (CI) were generated based on 5,000 bootstrap resamples, and CIs were presented along with p-values to interpret the significance of interaction/moderation effects. As recommended, moderation effects were considered significant in the case zero was not included within the CIs. Bootstrapping has been widely recommended because it improves power, but it was estimated that our sample size would be sufficient in order to detect medium-to-large effects using bootstrapping with two independent variables (IVs), an alpha set to .05, and a power of .80.[43]

4.0. Results

4.1. Descriptive statistics

Descriptive statistics are presented in Table 1. In the present sample, 64 % (n = 122) of participants were taking opioids (average daily opioid dose = 101.0 morphine equivalents; SD = 114.8).

Prior to conducting primary analyses, the potential confounding influence of ethnicity, clinical pain intensity, pain interference, and pain duration on primary study

variables (i.e., CPM, TS) was examined. For opioid users, the influence of daily opioid dose on CPM and TS was also examined. None of these variables were significantly associated with either CPM or TS (see Table 2). Opioid users and non-users differed significantly on measures of clinical pain intensity ($t(176) = -7.3$, $p < .01$) and pain interference ($t(154) = -8.4$, $p < .01$), but not in pain duration.

4.2. Association between psychological factors and endogenous pain modulation

Table 2 also shows the correlations between psychological factors and endogenous pain modulation measures. Correlational analyses revealed a marginally significant negative association between catastrophizing and CPM ($r = -.14$, $p = .05$), indicating that higher levels of catastrophizing were associated with lower CPM. A significant positive correlation was found between catastrophizing and TS ($r = .15$, $p < .05$). Depressive symptoms were not significantly associated with either CPM or TS.

Independent samples t-tests were used to examine whether CPM and TS scores varied as a function of participant sex (i.e., men/women) and opioid status (i.e., opioid users/non-users). Results indicated that there were no significant sex differences either in CPM ($t(188) = 1.8$, NS) or TS ($t(188) = -.62$, NS). Results of t-tests, however, indicated a marginally significant difference in CPM as a function of opioid status, with lower CPM scores for opioid users than non-users, $t(188) = 2.1$, $p < .05$. Opioid users and non-users did not differ significantly on the TS index, $t(188) = -0.10$, NS (see Figures 1 and 2).

4.3. Association between CPM and TS

A Pearson correlation was computed to examine the association between CPM and TS. Results revealed a significant negative correlation between CPM and TS

scores (r = -.20, p < .01), indicating that higher levels of CPM were associated with lower levels of temporal summation.

4.4. Moderators of the association between CPM and TS

As noted previously, five distinct bootstrapped moderation analyses were conducted to examine whether age, sex, opioid status, catastrophizing, or depressive symptoms moderated the association between CPM and TS. Results from these analyses indicated no significant 2-way interactions between CPM and participant age (B = .001, SE = .004, NS), sex (B = .053, SE = .099, NS), catastrophizing (B = -.006, SE = .004, NS), or depressive symptoms (B = -.001, SE = .006, NS). The two-way interaction effect between CPM and opioid status, however, was significant (B = .194, SE = .091, p < .05; LLCI = .014; ULCI = .375), indicating that the association between CPM and TS was moderated by participants' opioid status. Simple slope analyses were subsequently conducted in order to probe the interaction of CPM and opioid status on TS. As can be seen from Figure 3, the association between CPM and TS varied as a function of participants' opioid status (i.e., opioid users vs non-users). Results revealed a significant association between CPM and TS for non-users (r = -.34, p < .01), but not for opioid users (r = -.08, NS).

5.0. Discussion

Results of this study indicated that greater endogenous pain-inhibitory capacity is associated with lower levels of pain summation. Further, a moderation analysis revealed that the magnitude of this association differed significantly as a function of participants' opioid status, with opioid use appearing to reduce the magnitude of the inverse relationship between CPM and TS. None of the demographic or psychologic variables

included in the present study were found to moderate the association between CPM and TS.

The association that was found between CPM and TS is generally consistent with heuristic models of endogenous pain modulation that implicitly assume a certain degree of concordance between measures of pain inhibition and facilitation [4, 20, 27, 66, 84, 86]. For instance, individuals exhibiting either high pain inhibition (high CPM), low pain summation (low TS), or both, have been collectively described as having an "antinociceptive" pain modulation phenotype, as opposed to a pro-nociceptive phenotype characterized by high TS and low CPM [40, 86]. It is also noteworthy that individuals with chronic pain conditions characterized by "dysfunctional" pain modulation tend to show both decrements in CPM and elevations in TS relative to controls [1, 8, 22, 23, 66]. On the basis of this model, one would expect an inverse association between indices of endogenous pain inhibition and endogenous pain facilitation, which is what we observed in the present study. In addition, two recent studies found that roughly 30 % of individuals with "normal" or "higher-than-average" CPM levels were characterized by low levels of TS [56, 75], which is also consistent with our results.

Interestingly, the present study found an association between measures of CPM and TS selectively among individuals who are not using opioids. While a number of factors might account for the altered association between CPM and TS among opioid users, our data suggest that this might be due at least in part to the potentially disruptive effects of exogenous opioids on individuals' endogenous pain-inhibitory capacity. Consistent with previous work [29, 59], we found that the magnitude of CPM was lower for opioid users than non-users, suggesting that opioid use might dampen the functioning

of endogenous pain-inhibitory systems. Interestingly, several recent experimental studies have found that acute opioid administration may enhance endogenous pain inhibition [2, 53], and other reports of short-term administration have suggested minimal effects [73]. Collectively, these findings may suggest that the impact of opioid use on indices of pain inhibition shows a biphasic time course, with acute potentiation of CPM followed by long-term decrements of CPM. There is now compelling evidence both from preclinical [15, 50] and clinical [77, 88] studies that opioid use, over time, may progressively lead to enduring neuroplastic changes at various levels of the central nervous system (CNS), including within neural pathways known to be involved in endogenous pain inhibition. To the extent that endogenous pain-inhibitory systems exert a modulatory influence upon pain summation [6, 25, 41, 81], opioid-induced disruption of pain-inhibitory function might compromise the expected association between pain inhibition and pain facilitation, as observed among opioid users included in the present study. Although speculative, a disruption of pain-inhibitory function as a result of repeated opioid use might contribute to enhanced descending facilitatory activity and, in turn, to opioid-induced hyperalgesia (OIH), a phenomenon observed both experimentally and clinically [16, 17, 49, 72]. The observational nature of our study design prevents from concluding that opioid use caused hyperalgesic responses (i.e., opioid-induced hyperalgesia). However, the significantly lower pain-inhibitory (i.e., CPM) function and heightened clinical pain intensity levels observed among opioid users compared to non-users provide partial support for this notion. Previous studies among individuals with chronic pain have also observed disruptions in CPM [28, 60, 90] and heightened clinical pain intensity levels [17, 18] among long-term opioid users. However, given that these studies were also based on

observational study designs, research will be needed to determine whether a disruption of the association between pain-inhibitory and pain-facilitatory mechanisms may contribute to the development of opioid-induced hyperalgesia among individuals who initiate opioid therapy.

The findings of the present study have not only implications for conceptual models of endogenous pain modulation, but also for the assessment of pain-modulatory profiles in treatment settings. For instance, the modest overlap (i.e., concordance) between measures CPM and TS suggests considerable inter-individual heterogeneity within each of the pain modulation profiles. Consequently, in clinic settings, these two measures should not be used interchangeably to derive inferences about individuals' pain modulation. The predictive consideration of both CPM and TS paradigms is likely to yield a more reliable and comprehensive assessment of pain modulation profiles [55]. Our findings also suggest that a certain "discordance" between measures of endogenous pain inhibition (i.e., CPM) and pain facilitation (i.e., TS) might be more particularly pronounced among specific subgroups of individuals with chronic pain, such as those using opioid medication. Given that the coupling of high pain inhibition and low pain facilitation is viewed as an optimal pain modulation profile (i.e., an "antinociceptive" PMP) with the potential for buffering against negative pain-related outcomes [25, 84, 86], the putative deleterious impact of opioids on individuals' pain modulation profiles should be considered over the course of treatment selection, either in the context of perioperative or chronic pain management. Future research should also examine whether the association between pain inhibition and pain facilitation is enhanced when individuals

are discontinuing or tapering off opioid medication, as well as the time course of these putative shifts in pain modulation produced by changes in opioid treatments.

A number of limitations must be considered when interpreting the present findings. First, this study report is based on a convenience sample, which limited our explanatory reach in accounting for some of the findings that were reported. Second, due to the cross-sectional nature of the study design, individuals' levels of CPM and TS were assessed only at a single point in time. While these two measures have been found to be relatively stable over time [11, 14, 42, 44, 52], future studies involving repeated assessment of CPM and TS would allow one to derive more reliable inferences about the magnitude of the association between these two forms of endogenous pain modulation. Third, participants in the present study were taking relatively high doses of opioids considering recent changes in opioid prescribing guidelines [24]. Daily opioid doses were neither associated with CPM nor TS, but further studies will need to determine whether our findings can be generalized to patients taking lower opioid doses. It will also be important to further evaluate the influence of opioid dose and opioid use duration to the functioning of endogenous pain modulation systems. Fourth, individuals taking non-opioid analgesic medications were not included in the analyses. While this may be seen as a methodological strength, as it permitted us to rule out the influence of non-opioid medication on endogenous pain modulation, this places limits on the generalizability of our findings. Fifth, we did not measure potentially important variables, such as the duration of opioid therapy or the recency of opioid use in relation to QST. Future studies should control for inter-individual differences in these variables as they might influence measures of pain modulation. Finally, CPM was derived only on

the basis of the cold pressor test and pressure pain stimuli. Replication of our findings using other methods or CPM paradigms (i.e., using other conditioning and/or test stimuli) [44] is warranted before drawing more firm conclusions regarding the association between CPM and TS.

Conclusion

Findings from the present study provide new insights into the association between endogenous pain-inhibitory and pain summation systems, showing an inverse relationship between CPM and TS among individuals with chronic pain. That is, those exhibiting higher levels of CPM showed lower levels of TS. While the coupling of high pain inhibition and low pain facilitation is viewed as an optimal endogenous pain modulation profile that may buffer against negative pain-related outcomes [25, 84], the present findings suggest that opioid use might disrupt endogenous pain-inhibitory function and, in turn, the association between endogenous pain-inhibitory (i.e., CPM) and pain-facilitatory (TS) systems. Given that an impaired association between pain-inhibitory and pain-facilitatory systems is expected to increase individuals' vulnerability to poor pain-related outcomes [25, 56, 84], further research will be needed to identify the factors that may impair the interrelationship between these endogenous pain modulatory systems. Research will also be needed to determine whether a disruption of the association between pain-inhibitory and pain-facilitatory mechanisms may contribute to long-term sensitization and hyperalgesic responses (i.e., opioid-induced hyperalgesia) among opioid users. Research in this area would provide additional insights into the potentially deleterious impact of opioids on endogenous pain

modulation systems, and would have implications for the management of individuals with pain conditions.

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Figure Legends

Table 1
Sample characteristics and descriptive data for main study variables

Table 2
Correlations among study measures

Table 3
Pressure pain thresholds and cold water pain during the conditioned pain modulation test

Table 4
Pinprick pain ratings during the temporal summation of pain test

Figure 1
Conditioned pain modulation scores for opioid users and non-users

Figure 2
Temporal summation of pain scores for opioid users and non-users

Figure 3
Association between conditioned pain modulation and temporal summation as a function of individuals' opioid status

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page # where this item is located:
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the	N/A

		number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	11

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(b) Describe any methods used to examine subgroups and interactions	10
		(c) Explain how missing data were addressed	9-10
		(d) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-13

	(*b*) Report category boundaries when continuous variables were categorized	
	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

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